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## PHARMACO-ECONOMICS AND PHARMACO-EPIDEMIOLOGY

# *Cost-Effectiveness of Losartan Versus Atenolol in Treating Hypertension—An Analysis of the LIFE Study from a Swiss Perspective*

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***Summary. Aims:*** **To determine the economic benefit of losartan versus atenolol in patients with essential hypertension from the perspective of the Swiss healthcare system.**

***Methods and results:*** **The cost-effectiveness of losartan versus atenolol in the treatment of hypertension was analyzed by applying the results of the LIFE study to the Swiss healthcare system using a decision analysis framework.**

**The cost-effectiveness shows the losartan cohort to provide an additional life expectancy of 0.05 years per patient compared to the atenolol cohort, over a mean follow-up period of 4.8 years. Losartan therapy in hypertensive patients produced net cost savings of CHF 24 per patient and per 4.8 years compared to atenolol from the perspective of the Swiss health care system. This result was robust after varying costs of medication, stroke, myocardial infarction and life expectancy.**

***Conclusion:*** **The use of a losartan-based regimen in hypertensive patients with left ventricular hypertrophy in Switzerland is net cost-saving compared with a atenolol-based regimen.**

***Key Words.*** **cost-effectiveness, medical economics, hypertension, stroke losartan, atenolol, LIFE**

## *Background*

Stroke is the second most common cause of mortality, after cardiovascular disease. The annual overall incidence of stroke is estimated at 127'000 in Germany, 112'000 in Italy, 101'000 in UK, 89'000 in Spain and 78'000 in France. Death related to stroke is declining in many countries (Finland, Sweden, France, Spain) and in both sexes. The incidence in Switzerland has been reported to be in the magnitude of 150/100'000/year [1].

In middle and late adult life, hypertension is undoubtedly the strongest modifiable risk factor for both ischemic and hemorrhagic stroke. Hypertension is present in approximately 70% of stroke cases. The risk of stroke rises in proportion to blood pressure, for males as well as for females, and almost doubles for every 7.5 mm Hg increment in diastolic blood pressure (DBP) [2].

Losartan (Cosaar®) represents one of the newer classes of antihypertensive agents with potential analogous efficacy based on evidence of reduction in cardiovascular events with ACE inhibitors and further, the evidence for a possibly greater effect in reduction in hypertensive left ventricular hypertrophy by ACE inhibitors than some other class of agents. Clinical studies have demonstrated that the frequency of side-effects in patients receiving losartan alone or in combination with hydrochlorothiazide (HCTZ) is similar to placebo [3,4].

The **L**osartan **I**ntervention **F**or **E**ndpoint reduction (LIFE) in Hypertension study was undertaken to determine whether losartan could be demonstrated to be more effective than a member of the betablocker class in decreasing morbidity and mortality in a relatively high risk hypertensive group [14]. It was a double-blind, randomized, parallel-group trial in 9'193 hypertensive patients with electrocardiographic (ECG) evidence for with a mean 4.8 year follow-up in LIFE to determine whether there was a difference in primary cardiovascular events between an angiotensin II receptor blocker (losartan) [Cosaar®], and a betablocker (atenolol) [Tenormin® and several other generic brands]. A substudy evaluated these differences in diabetics. With a similar reduction in blood pressure, primary events (cardiovascular morbidity and death) occurred in fewer participants in the losartan group (23.8/1'000 patient-years) than the atenolol group (27.9/1'000 patient-years) (adjusted hazard ratio: 0.87; 95% CI: 0.77–0.98). Similar results were found in the diabetic substudy with 39.2/1'000 patient-years in the losartan group versus 53.6/1'000 patient-years in the atenolol group (adjusted hazard ratio: 0.76; 95%

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CI: 0.58–0.98). The stroke reduction drove the primary endpoint difference. There was a highly significant 25% reduction in the incidence of fatal/nonfatal stroke in the losartan-treated patients (adjusted hazard ratio 0.75; 95% CI: 0·63–0·89).

The results of the main study indicated a significant benefit in the losartan group [14]. Event-free survival was reported in 85.5% of the losartan group (35.6/1000 patient-years) and 83.6% (31.4/1'000 patient-years) of the atenolol group ($p = 0.04$) [5]. Blood pressure, initially 174/98 mm Hg in both groups, was comparably reduced (144/81 mm Hg and 145/81 mm Hg at last visit). Analysis for components of the primary endpoint showed a benefit for losartan mainly for stroke but no significant difference in myocardial infarction. The losartan group had an 11% reduction in cardiovascular mortality but this reduction was not statistically significant (adjusted hazard ratio 0.89; 95% CI: 0.73–1.07). The overall drop-out rates were 2.2% for Losartan treated patients and 2.0% for atenolol patients. Adverse events causing dropout from the study were more common in the atenolol group (18% vs. 13%). This difference was statistically significant ($p < 0.0001$). New onset diabetes developed in 6% of the losartan group vs. 8% of the atenolol group (adjusted hazard ratio 0.75; 95% CI: 0.63–0.88).

To use the existing resources optimally, the cost-effectiveness of the different treatment methods must be known and taken into consideration. Defining and measuring the cost-effectiveness of a treatment is difficult. The instruments of evaluation research (e.g. benefit-risk analysis, cost-effectiveness analysis) must be used for the evaluation of the efficiency of medical treatments. Assuming that the outputs of such analyses are the same (e.g. costs per life-year saved), one then has the ability to compare different treatments with each other.

Despite recent guidelines emphasising the need for aggressive treatment in patients with elevated blood pressure, the control of hypertension in Europe and the USA is poor, imposing a considerable burden in terms of patient morbidity and mortality, and associated healthcare costs. The cost-effectiveness of losartan in the treatment of patients with diabetic nephropathy has already been demonstrated by Sandoz et al. based on a Swiss model [6]. As atenolol is among the most widely prescribed antihypertensives (326'000 annual prescriptions for atenolol among a total of 700'000 for betablockers and 4 mio. for all antihypertensives) in Switzerland, a comparison with Losartan is appropriate and hence essential for policy making.

## Study Objective

The purpose of the following study is to answer the ensuing question: How cost-effective is losartan versus atenolol in 60 year old patients with essential hypertension from the perspective of the Swiss healthcare system?

## Methods

### Study design

Cost-effectiveness analysis was chosen for the purpose of this study. In contrast to cost-benefit analysis, non-monetary parameters e.g. the number of life-years saved are included in the economic assessment as benefit or output criteria. This ensures that the economic efficiency of a treatment is evaluated with due consideration to the medical success.

The present analysis is retrospective. The results of the already published double-blind, randomised, controlled clinical trial LIFE (Losartan Intervention for Endpoint reduction in Hypertension) (Table 1). This trial was conducted in six European countries and the US and was used as the basis of efficiency assessment [7]. It was assumed that the effects on clinical outcomes can be transferred to Switzerland.

A brief comparison of the effects on clinical outcomes of the LIFE study of the losartan and atenolol groups for some particularly cost-relevant clinical events is shown in Table 2. A detailed description of study design has been published elsewhere. A review of the design of the LIFE trial has been published extensively [8].

### Economic study endpoint

The intended endpoint of this cost-effectiveness analysis of losartan therapy is the incremental cost per life-year gained in Switzerland expressed in Swiss francs (CHF).

### Determination of costs and effectiveness

*Costs.* The costs are based on the cost incurred by the social health insurance providers. Specifically, only prices that are reimbursed were taken into consideration. For the determination of the total costs of losartan treated group, three directly attributable cost groups were included: (1) the medication costs for losartan according to the dosage used in the LIFE study, (2) the acute costs and 2 year follow-up of a myocardial infarction and (3) the acute and 2 year follow-up costs of a stroke. Indirect costs (e.g. costs related to loss of work) and intangible costs (e.g. pain) were not included in this calculation.

The costs of treatment with losartan were based on pharmacy prices in Switzerland [9], because mainly pharmacies are authorized to sell drugs to ambulatory patients. We calculated mean daily treatment costs on the basis of the mean daily dosages used in patients in the intent-to-treat population, i.e. 82 mg/d for losartan and 79 mg/d for atenolol. A patient co-payment of 10% was deducted from the pharmacy price. The total

***Table 1.*** *Design of the LIFE study*

| | |
|---|---|
| Objectives | To establish whether selective blocking of angiotensin II improves left ventricular hypertrophy beyond reducing blood pressure |
| | To establish whether selective blocking of angiotensin II reduces cardiovascular morbidity and mortality |
| Study design | Multicentre, double blind, randomised, placebo-controlled study in 945 centers in Scandinavia, England and the United States |
| Inclusion criteria | Hypertension: sitting blooding pressure systolic 160–200 mmHg, diastolic 95–115 mmHg |
| | ECG diagnosis of left ventricular hypertrophy (Cornell voltage or Sokolow-Lyon Index) |
| | Age: 55–80 years |
| Exclusion criteria | Secondary hypertension |
| | Myocardial infarction, cerebrovascular insult 6 months prior to study, angina pectoris requiring betablocker treatment, LV ejection fraction <40% |
| Intervention | 1–2 week placebo run-in phase |
| | Losartan 50 mg/d, titrated to 100 mg/d, if necessary with 12.5 hydrochlorothiazide |
| | Atenolol 50 mg/d, titrated to 100 mg/d, if necessary with 12.5 hydrochlorothiazide |
| Endpoints | *Primary:* combined endpoint death, myocardial infarction, stroke |
| | *Secondary:* total mortality, angina pectoris, new onset diabetes, coronary or peripheral vascularisation |
| Period of observation | 4 years |
| Patients | 9'193 patients, average age 66.9 years, 54% women |
| | *Losartan group*: 4'605 patients, average age 66.9 years, 54% women, history of vascular disease 26%, smokers 16%, diabetes 13%, mean blood pressure 174.3/97.9 mmHg |
| | *Atenolol group:* 4'588 patients, average age 66.9 years, 54% women, history of vascular disease 24%, smokers 17%, diabetes 13%, mean blood pressure 174.5/97.7 mmHg |

***Table 2.*** *Comparison of treatment effects in the LIFE study*

| Group | Losartan (Rate/1000/ year) | Atenolol (Rate/1000/ year) | Adjusted hazard (ratio (95% confidence limits) |
|---|---|---|---|
| Primary composite endpoint[+] | 23.8 | 27.9 | 0.87 (0.77–0.98) |
| Cardiovascular mortality | 9.2 | 10.6 | 0.89 (0.73–1.07) |
| Stroke | 10.8 | 14.5 | 0.75 (0.63–0.89) |
| Myocardial infarction | 9.2 | 8.7 | 1.07 (0.88–1.31) |
| New onset diabetes mellitus | 13.0 | 17.4 | 0.75 (0.63–0.88) |

[+]Cardiovascular mortality, stroke, and myocardial infarction.

***Table 3.*** *Costs in the losartan and atenolol groups per 1000 patients over 4.8 years in Swiss Francs*

| Group | Losartan | Atenolol | Difference (95% confidence limits) |
|---|---|---|---|
| Medication cost with 82 mg/day losartan and 79 mg/day atenolol | 2'620'397 | 797'749 | 1'822'648 |
| Cost of myocardial infarctions | 1'579'852 | 1'505'620 | 74'232 (−180'674; 466'742) |
| Cost of ischemic strokes | 5'722'442 | 7'649'942 | −1'927'500 (−2'830'479; −841'494) |
| Total costs per 1'000 patients | 9'922'691 | 9'953'311 | −30'620 (−1'188'505; 1'447'896) |
| Discounted at 5% per year | | | −24'227 (−940'356; 1'145'589) |

drug costs were CHF 2.62 million per 1'000 patients, based on a daily treatment cost of CHF 1.50 for losartan and CHF 0.46 for atenolol and a median treatment period of 4.8 years. Hydrochlorothiazide and additional drug costs were not valued, because they did not differ significantly between the groups.

These total medication costs were projected assuming a patient compliance rate of 100% throughout the treatment period. As it may be assumed that the acquisition costs for losartan also apply to those study patients who no longer take the medication and as less than 9% of patients died during the observation period the medication costs were calculated for 100% of the patients (Table 3).

The Swiss-based costs of an acute myocardial infarction and of a stroke (medication costs, interventions, hospitalisation, out-patient treatment, rehabilitation), have previously been calculated by an international study group. In this analysis, the direct medical costs of ischemic strokes and myocardial infarctions were evaluated using a decision analysis model, supplemented with information from local Delphi panels [10]. In brief, these calculations covered the acute care costs from a health care system perspective, including follow-up health care resource utilisation (in- and outpatient) for 24 months after the index hospitalisation.

The acute care costs per patient with stroke resp. myocardial infarction were CHF 28'305 resp. 24'972. The corresponding follow-up costs were CHF 85'281 resp. 11'772. These costs were all adjusted to 2003 values, taking into account inflation.

In order to determine the treatment costs that could be avoided by the use of losartan, the avoidable events per 1'000 patients over three years were taken from the LIFE study and multiplied by the treatment costs of each individual treatment and over the study period of 4.8 years [11]. Only costs were discounted at a base discount rate of 5% which is the standard rate applied for health care investments in Switzerland and which is supported by the recommendations by the Swiss Office of Social Insurance [12].

*Effectiveness.* In this economic analysis, the criterion for effectiveness is represented by the life-years gained in the group treated with losartan, compared to the group that received atenolol. Even though the LIFE trial did not yield a statistically significant reduction in cardiovascular morbidity (a secondary endpoint), we projected survival beyond the trial period to incorporate the full effects of stroke on survival. Estimation of the average life expectancy of hypertensive patients was based on the DEALE method [13,14], using the all-cause mortality of Swiss population analogous to the LIFE population in terms of age and gender distribution [15]. In 2000, the average life expectancy of a 60 year old Swiss person was 76.2 years for men and 82.3 years for women [32]. On this basis, the remaining life expectancy of persons with a mean age of 66.9 years is therefore 11.8 years. The LIFE study reports a disease-specific over-mortality in the atenolol group of 0.0847 per patient. This figure is used as the disease-specific excess mortality. By linking both mortality rates according to the DEALE method, the adjusted life expectancy, can be calculated to be 11.04 years [30,31].

*Cost-effectiveness of losartan treatment.* The costs per life-year saved can be calculated by dividing the discounted cost difference between the losartan and the atenolol group by the number of life-years gained in the losartan group.

*Sensitivity analyses.* Sensitivity analyses were performed in order to test the accuracy and sensitivity of the results (i.e. the costs per life-year saved). For this purpose and for simplicity only the medication costs for losartan, the treatment costs for the events observed and the approximated life expectancy were varied by ±20%. We judge these to be the most important, costly parameters. Because the discount rate of 5% can vary too, we calculated the cost-effectiveness for a discount rate between 3 and 7%.

## Results

Table 3 shows the individual costs in the following cost groups: daily treatment costs, costs of myocardial infarction and stroke in the group treated with losartan and in the atenolol group. It is clear that there is an additional medication cost of approximately CHF 1'823 per patient over 4.8 years in the losartan group compared to the atenolol group. In contrast, a savings potential can be seen in the losartan group, as the costs of the most expensive endpoint stroke are reduced. Total costs of approximately CHF 9'923 can be calculated for a patient treated with losartan over 4.8 years. Total costs in a patient treated with atenolol are CHF 9'953. Thus, the total cost difference in favour of losartan are nominal CHF 31 (95% CI: −1189; 1448), resp. discounted CHF 24 (95% CI: −940; 1146).

The calculation of effectiveness showed an additional life expectancy of 0.0495 years in the losartan cohort in comparison to the atenolol group over a period of observation of 4.8 years (Table 4).

The primarily intended cost-effectiveness analysis of losartan treatment made no more sense due to equivalence between the groups. The net savings achieved

***Table 4.*** *Expected additional life expectancy due to losartan therapy*

| | |
|---|---|
| Average age of patients at baseline in LIFE study | |
| Losartan group | 66.9 years |
| Atenolol group | 66.9 years |
| Normal life expectancy in Switzerland | |
| Men | 76.2 years |
| Women | 82.3 years |
| Life expectancy study population, weighted | |
| (Study population: 59% men, 41% women) | 11.8 years |
| Weighted mortality rate per patient year | 0.0847 |
| Expected fatal cases in atenolol group | 32.5/1'000 |
| Disease specific mortality rate per annum | 0.00847 |
| Adjusted mortality | |
| Adjusted average mortality (DEALE) | 0.0906 |
| Remaining life expectancy (DEALE) | 11.04 years |
| Expected fatal events | |
| Losartan | 28.01/1'000 patients |
| Atenolol | 32.50/1'000 patients |
| Cases prevented | 4.48/1'000 patients |
| Years of Life Saved (YOLS) per 1'000 Patients | |
| (Prevented cases /1'000 Patients × remaining life expectance of study population) | 4.48 × 11.04 = 49.51 years |
| Incremental life expectancy of losartan treatment in comparison to atenolol | 0.0495 years/patient |

*Declining Exponential Approximation of Life Expectancy.

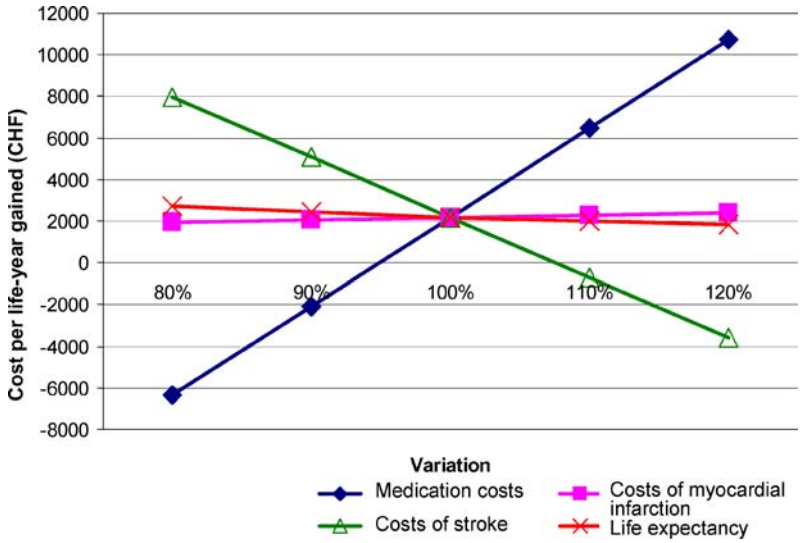


***Fig. 1.*** *Univariate Sensitivity analysis: Effect of variation of key input variables on cost-effectiveness ratio.*

with losartan of approximately CHF 31 per patient yields losartan as an economically dominant option. The calculation as a ratio of cost per life-year saved hence makes no sense.

The results of the sensitivity analysis (Fig. 1) confirm that the estimated net savings are maintained over a large range of variation of the input variables. Discounting at 3% resp. 7% revealed a cost difference in favour of losartan of CHF 27 (95% CI: −1031; 1256) resp. CHF 22 (95% CI: −859; 1046). In the worst case, a theoretical cost-effectiveness ratio would be CHF 25336 per lifeyear gained, which would still be considered a worthwhile health care investment. Table 5 displays the cost-effectiveness of selected health care interventions.

***Table 5.*** *Cost-effectiveness of selected cardiovascular interventions*

| Intervention | Cost per life-year saved in Swiss Francs | Source |
|---|---|---|
| Losartan versus atenolol in hypertension (LIFE Study) | <0* | Present study |
| Lisinopril in congestive heart failure (ATLAS) | <0* | Ess S et al. [19] |
| Captopril after myocardial infarction (SAVE) | 1'600 | Szucs T, Berger K, Schulte-Hillen J, Kleber FX [20] |
| Beta-blockers for post-myocardial infarction patients at high risk | 3'600 | Goldman L, Sia ST, Cook EF, Rutherford JD, Weinstein MC [21] |
| Pravastatin therapy for CHD patients with slightly increased cholesterol values (LIPID) | 6'985 | Szucs et al. [22] |
| Pravastatin therapy for CHD patients with increased cholesterol values (PLAC I/II) | 12'800 | Berger K, Klose G, Szucs T [11] |
| Low cholesterol diet for men aged ≥60 years with a cholesterol value of 180 mg/dl (4.7 mmol/l) | 14'480 | Taylor WC, Pass TM, Shepard DS, Komaroff AL [23] |
| Amlodipine therapy for CHD patients with normal cholesterol (PREVENT) | 14'650 | Cathomas G, Erne P, Szucs TD [24] |
| Pravastatin therapy for CHD patients over 60 years with normal cholesterol values (CARE) | 18'400 | Berger K, Klose G, Szucs TD [11] |
| Antihypertensive agents for patients aged ≥40 years with diastolic blood pressure levels ≥105 mm Hg | 19'280 | Stason WB, Weinstein MC [25] |
| Beta-blockers for post-myocardial patients at low risk | 20'400 | Goldman L, Sia ST, Cook EF, Rutherford JD, Weinstein MC [26] |
| Hypertensive patients with multiple risk factors (ASCOT) | 20'003 | Szucs TD, Muller D, Darioli R. [26] |
| Clopidogrel in coronary secondary prevention (CAPRIE) | 24'705 | Haldemann R et R et al. [27] |
| tPA for myocardial infarction (GUSTO IV) | 39'440 | Mark DB, Hlatky SB, Davis CE [28] |

*Values <0 denotes net savings, i.e. a dominant economic strategy.

## Discussion

Using the example of Losartan, the economic assessment of angiotensin II antagonists in hypertensive patients with LVH has shown that the administration of this medication is a highly economically viable option with net savings. The benefits of Losartan are attributed almost exclusively to the prevention of stroke. However, the economic performance of a medical intervention can never be judged in isolation, but must always be seen in comparison to other interventions and should be discussed in relation to this background. The positioning of the results in the context of the cost-effectiveness of other interventions is shown in Table 5, and makes it clear that treatment with losartan is in a more favourable range, than can be attained by some other broadly accepted interventions.

To the best of our knowledge, the current article is the first published economic analysis based on the LIFE study. As this is a retrospective analysis, and benefits were not directly recorded, it was not possible to carry out a cost-utility analysis. Such an analysis specifies costs in monetary units and consequences as benefit, i.e. as a quantity that reflects the preferences of the affected target group for a state of health (e.g. quality-adjusted life-years).

A limitation of the present analysis is certainly that the results of the LIFE study, that was conducted in the USA, the United Kingdom and Scandinavia were transferred to the situation in Switzerland, and that the estimated life expectancy of CHD patients in Switzerland was used for the calculation of cost-effectiveness. There are indications that the influence of other risk factors may possibly vary in the degree of severity to which they affect the Swiss population compared with the original study population. For this reason, the estimated life expectancy was also varied in the sensitivity analyses. On the other hand, the patient population of the LIFE study is comparable to a Swiss hypertension population with respect to age, co-morbidity and concomitant medication [16]. It should also be pointed out that patients in the LIFE study are only partly representative of the total collective of hypertensive patients in Switzerland: as always, study patients are naturally carefully selected in terms of co-morbidity, compliance and quality of care. In this respect, the results of the LIFE study correspond to the best case scenario. Furthermore, LIFE did not differentiate individually between non-fatal and fatal events, as this endpoint was defined, recorded and analysed as a combined endpoint in the LIFE study.

We believe that the LIFE trial represents an important body of evidence requiring a health economic assessment. Even though the impact of Losartan on the endpoint myocardial infarction was not significant, the endpoint stroke represents an extremely expensive endpoint for the Swiss health care system. Additional analyses of the LIFE trial further emphasize the benefit of losartan compared with atenolol, in moderately hypertensive patients without overt vascular disease, demonstrating that the benefit of losartan in this population is independent of the drug's blood pressure lowering effect. Devereux et al. have now shown even greater reductions in both the composite endpoint and the components of the primary endpoint for losartan compared with atenolol in patients who had no overt vascular disease and which were therefore at lower risk [17].

At this point it should again be stressed that the present calculation model for Switzerland follows an extremely conservative approach. Potential savings in the avoidance of intensive care, loss of working time or rehabilitation measures can only be surmised but not quantified and evaluated. In the losartan studies that have been carried out to date, no data has been given with respect to differences in the patients' quality of life, differences concerning necessary rehabilitation measures and the variable number of early retirements and lost working days in the losartan and atenolol groups. As it may be assumed that these costs are not inconsiderable in amount, further potential savings could be exploited by using more effective and efficient therapeutic strategies. Moreover, the low incidence of side effects with losartan in comparison to other drugs that are effective in secondary prevention was not included in the calculations.

Another reason, why our estimates are likely to underestimate the true economic value of losartan is that we did not value the benefits of losartan in reducing the new onset of diabetes. Our group has determined that the mean annual per patient costs of type 2 diabetics in Switzerland are approximately CHF 3'500 [18]. These avoidable costs may thus be factored into the overall equation and may contribute favourably to the numerator of the cost-effectiveness ratio of the present study. This clinical benefit is extremely important also from a public health perspective.

It also has to be considered that our cost analysis is a "within trial" analysis, that is, costs are limited to the study duration of the LIFE trial. Only a 2-year follow-up of the costs of the first index event was used to take into account possible sequelae, e.g. rehospitalisations. As a result, potential costs and benefits that occur after more than the mean follow-up of 4.8 years are not included in the calculations.

A further limitation of this study is the assumption of a 100% compliance of drug treatment and the omitting of hydrochlorothiazide costing. As we did not have access to the raw data set, we were not able to determine the economic impact in a pragmatic sense without serious modelling. However, given the metabolic side-effect profile of hydrochlorothiazide, the costs of new-onset diabetes will likely reverse the economics of this non-expensive drug class.

Economic evaluations are of practical relevance for the general practitioner to the extent that the conscious use of economical medical therapies reduces their fear

and uncertainty about budget adherence and recourse, and justifies his prescribing practice. In addition, the use of efficient medical therapies offers the individual doctor some relief for their medicines budget, e.g. by reducing the prescriptions of concomitant medications, and a greater individual manoeuvrability within the framework of the fixed prescription budget allocated to them.

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